ERD European Journal of Research in Dentistry

REVIEW / DERLEME

Effects of Interleukin 6 (rs1800795) and Other Proinflammatory Interleukins Gene Polymorphisms in Periodontal Diseases: A Brief Review

İnterlökin 6 (rs1800795) ve Diğer Proinflamatuar İnterlökin Gen Polimorfizmlerinin Periodontal Hastalıklardaki Etkileri: Kısa Bir Derleme

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Article History

Submitted	05.04.2025
Revised	14.04.2025
Accepted	18.04.2025
Published	30.04.2025

ABSTRACT

A disease evaluated in medicine can be a predictor for a disease in dentistry, and a disease in dentistry can be a precursor to a disease in medicine. An example is the relationship between cellular immune factors, which are a field of the immune system, and "peri-implant diseases" evaluated in the dentistry literature. The increase in the quality of life and life span in people necessitates the research of new treatment methodologies for oral and dental health in the oral rehabilitation process. Peri-implant diseases are one of the important issues to investigate. There are many factors such as the genetic structure of the individual, and microbiological and environmental factors that determine the success and effectiveness of implant treatment. Knowing the infrastructure of immune-related proinflammatory cytokines in the peri-implantitis disease that we have examined can contribute to the effectiveness of treatment approaches related to this disease. For this reason, we aimed to a brief review of studies evaluating the effectiveness of the IL-6 rs1800795 gene polymorphism, an important proinflammatory cytokine, and the IL-1, IL-8 and IL-17 polymorphisms, which are other proinflammatory cytokines evaluated in the interleukin class, on peri-implantitis and therefore periodontal diseases.

Keywords: Peri-implantitis, interleukin-6, interleukins, proinflammatory cytokines, genetic polymorphism

ÖZ

Tıp alanında değerlendirilen bir hastalık diş hekimliği alanındaki bir hastalık için prediktör olabileceği gibi diş hekimliği alanındaki bir hastalık tıp alanındaki bir hastalığın öncüsü olabilir. Bunun bir örneği bağışıklık sisteminin bir alanı olan hücresel bağışıklık faktörlerinin diş hekimliği literatürü içerisinde değerlendirilen "implant çevresi hastalıkları" ile ilişkisidir. İnsanlarda yaşam kalitesinin ve yaşam sürecinin artması ile oral rehabilitasyon sürecinde ağız ve diş sağlığına yönelik yeni tedavi metodolojilerini araştırmasını zorunlu hale getirmektedir. İmplant çevresi hastalıkları araştırılması önemli olan konulardan birisidir. İmplant tedavisinin başarısını ve etkinliğini belirleyen bireyin genetik yapısı, mikrobiyolojik ve çevresel faktörler gibi birçok etmen bulunmaktadır. İncelemesini yapmış olduğumuz peri-implantitis hastalığında bağışıklıkla ilişkili proinflamatuar sitokinlerin alt yapısını bilmek bu hastalıkla ilgili tedavi yaklaşımlarının etkinliğine katkı sağlayabilir. Bizde bu bağlamda önemli bir proinflamatuar sitokin olan IL-6 rs1800795 gen polimorfizminin ve interlökin sınıfında değerlendirilen diğer proinflamatuar sitokinlerden olan IL-1, IL-8 ve IL-17 gen polimorfizmlerinin peri-implantitis ve dolayısıyla periodontal hastalıklar üzerine etkinliğini değerlendiren çalışmalardan kısa bir derleme çalışmasını sizlere sunmayı hedefledik.

Anahtar Kelimeler: Peri-implantitis, interlökin-6, interlökinler, proinflamatuar sitokinler, genetik polimorfizm

How to cite this article: İn G. Effects of Interleukin 6 (rs1800795) and Other Proinflammatory Interleukins Gene Polymorphisms in Periodontal Diseases: A Brief Review. *European Journal of Research in Dentistry*, 2025;9(1): 71-76. DOI: http://dx.doi.org/10.29228/erd.96

INTRODUCTION

Treatment approaches in the field of dentistry have necessitated the implementation of new methods for the development of optimal oral rehabilitation, especially for partial or complete tooth loss. In parallel with the increasing quality of life, it has become an important public health issue (Müller et al., 2017). It is also stated that the prevalence of dental implants use worldwide will reach 23% by 2026 (Moraschini et al., 2015). However, oral rehabilitation approaches aimed at implantology cause periodontal and peri-implant-related biological complications, especially periimplantitis (PI), to be frequently observed (Lee et al., 2017).

In the 2017 World Workshop, Peri-implant Diseases were classified as Implant Mucositis, PI, and Soft, Hard Fabric Defects for Dental Implants. Peri-implant Diseases were classified as Implant Mucositis, PI, and Soft, Hard Fabric Defects for Dental Implants. The definition of implant disease required reorganization. PI was defined as inflammation in the tissues of dental implants and plaque formation associated with indirect bone loss (Berglundh et al., 2018). Furthermore, implantitis affects more than 45% of dental implant patients (Lee et al., 2017). Patients diagnosed with periodontitis (Dreyer et al., 2018).

Among the main risk factors, the formation of bacterial plaques is defined as the major pathogenesis of peripheral inflammation. Clinical studies using polymerase chain reaction technology (PCR) have shown that periodontal pathogenicity such as *Aggregate actors Actinomycetencomatone, Porphyromonas-givalis, Treponemer-denticola,* and *Fusobacterium-nucleatum* are transmitted by natural perpetrators. Periimplant flora is mostly similar, but the bacterial community involved in the development of Periimplant flora has a wider spectrum (Sahrmann et al., 2020). Microbiota are relatively well known for terminal lobe periimplantitis, but in the case of genetic activity in inflammatory cell immunity, information on genetic activity is more limited. In addition, it has been observed that not all patients with one or more of the basic risk factors develop PI. Also, the potential of genetic susceptibility to be an important factor in the development of PI suggests that it may open new avenues of research in this area (Lee et al., 2014).

Genetic polymorphisms are characterized by variation in nucleotide sequences at specific locations in DNA and are seen in at least 1% of the population. The most common of these variations are single nucleotide polymorphisms (SNPs), which refer to genomic regions where a single base varies between alleles (Smith et al., 2005). SNP detection can-be-used to identify-altered gene or-proteins in-a particular-disease. In particular, the SNPs in these genes have become widespread, as cytokine genes play a significant role in regulating immune response mechanisms (Taylor et al., 2000). Bacterial containmen for dental implant disease occurs several weeks after the implant is placed by microorganisms available in the oral cavity. Bacterial products from pathogens formed around dental tissue stimulate the production of mediators secreted in the periimplant crevicular fluid, which destroy periimplant tissues. *Tumor necrosis factor-alpha* (TNF-a), IL-1, IL-6, IL-8, IL-17, and prostaglandin E_2 are cytokines that have been observed to be associated with dental diseases (Melo et al., 2012; Huang et al., 2024) (*Fig. 1*).

To evaluate and understand the pathogenesis of periodontal and peri-implant diseases, cytokines, chemokines, growth factors and their receptors involved in the host response in periodontal and peri-implant tissue should be evaluated. This review was prepared to examine the effectiveness of the *IL-6 rs1800795* gene polymorphism, which is a proinflammatory interleukin, and certain interleukin gene polymorphisms evaluated and investigated in the proinflammatory interleukin class in patients diagnosed with PI.

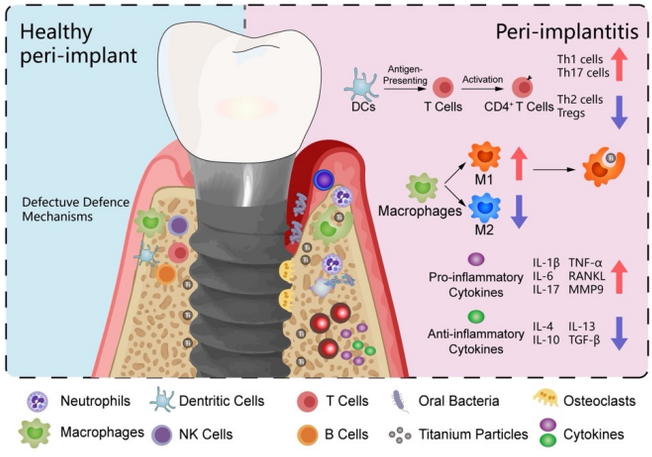

Figure 1. Peri-implant microenvironment. (Huang et al., 2024)

The Role of Interleukin 6 (rs1800795) Gene Polymorphism in Periodontal Diseases

IL-6 is a protein molecule that-plays a very important role-in-the immune-system as a proinflammatory-cytokine and is also an-important cytokine found in non-immune cell populations. It also plays a role in the regulation of immunity and inflammation by acting as an intercellular messenger signalling molecule (Tanaka et al., 2014). IL-6 stimulates several biological processes, including antibody-production, T cell-activation, B-cell-differentiation, increased acute phase protein, increased hematopoiesis, induction of angiogenesis, vascular permeability, and osteoclast differentiation. Therefore, IL-6 has a significant effect on the response to microbial attacks and not only acts as an anti-inflammatory tool, but also as an anti-inflammatory tool when the inflammatory process becomes chronic (Chmielewski et al., 2023).

It was reported that changes in systemic cıncentration of cytosin and mirror correlate with disease severity in the presence of periodontitis where IL-6 expression is assessed by investigating peripheral blood cells (Melo et al., 2012). Furthermore, studies have

reported that IL-6_expression in saliva-and-gingival-fluid increases in periodontitis-patients (Mazurek-Mochol et al., 2024) and increases peri-implant IL-6 concentrations (Chmielewski et al., 2023).

IL-6 rs1800795 polymorphism is formed by the replacement of guanine (G) nucleotide with cytosine (C) nucleotide. The presence of the positive allele, G, is related to periodontal disease (Lin et al., 2007).

In a 2010 study in which 38 geriatric participants with moderate and severe chronic periodontal disease were evaluated, it was observed that the *IL-6 rs1800795* polymorphism, especially the GG genotype, may play a part in chronic periodontal disease in the Brazilian population (Costa et al., 2010). This result supports the study conducted in Finland in 2007, in which the *IL-6 rs1800795* polymorphism in individuals with moderate chronic periodontitis was observed to be dominant in the GG genotype (Tervonen et al., 2007). A meta-analysis study published in 2016, including 21 case-control studies, reported that the *IL-6-174* GG genotype is associated with chronic periodontal disease in Brazilian and Caucasian populations. The same study, In the Asian population, it has been reported that there are conflicting results regarding whether the CC genotype is effective (Zhu et al., 2016).

Other case studies in Caucasian and Asian populations have reported that the *IL-6-174* G/C polymorphism, GC genotype, a protective factor for periodontitis (Gabriela et al., 2014; Fan et al., 2011). In addition, studies in the Chinese population have reported that this polymorphism is rare (Fan et al., 2011). In a study published in 2024 and conducted on the Brazilian population, it was observed that the relationship between the *IL-6 rs1800795* polymorphism and the risk of periodontitis was not correlated with selected clinical parameters. No interaction was found between IL-6 expression in gingival tissue and plaque index in healthy subjects, indicating that IL-6 may play a protective role against bacterial colonization and plaque development (Mazurek-Mochol et al., 2024).

A study in the British population reported that the C allele of the *IL-6-174G/C* gene polymorphism was associated with lower IL-6 levels in health problems such as juvenile chronic arthritis, while A study in the Brazilian population of individuals with periodontitis reported that the *IL-6-174G/C* gene polymorphism, which was more common in the control group, was associated with increased IL-6 expression for the CC genotype. The opposite observation was that in the German population, the CC genotype was associated with a higher risk of developing periodontitis (Fishman et al., 1998; Moreira et al., 2007).

The Role of Interleukin 6 (rs1800795) Gene Polymorphism on Peri-implantitis

The periodontal diseases examined are homeostatic imbalances resulting from microbial pathogens and are diseases with similar patterns (Turkmen et al., 2022). Considering the genetic origins of periodontitis and PI patients, the host response is extremely important.

In implantitis, proinflammatory cytokines promote local secretion of *Metalloproteinase* (MP). This causes damage to implant tissues and bone destruction. Especially IL-6 is a cytokine with pleiotropic effects secreted in the early phase of the immune response (Petkovic-Curcin et all., 2017).

There are a limited number of studies addressing the relationship between *IL-6 – 174* gene polymorphism and PI risk. Melo et al. published a study (2012), examining patients diagnosed with PI and healthy individuals, and reported that the most common allele for *IL6 – 174* polymorphism was G and the most common genotype was GG, and although this allele and genotype were observed more in both groups, they stated that there was no statistically significant difference between the groups. However, in the literature, a polymorphism study evaluating osseointegrated implants reported that *IL6-174* gene polymorphism was observed less, especially in peri-implant disease. In a study evaluating from this perspective, they found that the distribution of alleles and genotypes of *IL6-174* G/C did not have a significant relationship with the early failure observed in dental implant treatment (Campos et al., 2005).

In a controlled study published in 2017 examining 98 participants who received implant treatment in the last 1 year, it was stated that the *IL-6 rs1800795* polymorphism differed in terms of genotype and allele frequency. In the evaluations within the groups, it was stated that the C allele may be protective due to incompatibilities in genotype distribution (Turkmen et al., 2022).

The findings of this published study support the idea that GG genotype can be a cause for PI and chronic periodontitis susceptibility with the results obtained from the Brazilian population, where 215 people were examined in 2013 (Casado et al., 2013).

Role of Gene Polymorphisms of Proinflammatory Interleukins in Peri-implantitis

Interleukins are proinflammatory cytokines, and they are effective in all processes related to periodontitis disease and osteoclastagenesis (Jia et al., 2015). Inflammation has a critical impact on osseointegration and implant success. Inflammatory cytokine production triggers PI and stimulates bone resorption, leading to implant failure.

IL-1 is known as the main cause of chronic inflammatory diseases and plays an effective role in the destruction of the extracellular matrix of the connective tissue and bone destruction (Cardoso et al., 2022). Moreover, it is the main pyrogen cytokine. It is considered one of the main cytokines in the inflammatory response because it affects other inflammatory cytokines. Mainly, IL-1β levels show an increase in peri-implant cervical fluid (PICF) in PI. In addition, IL-1β levels have been reported to be positively correlated with implant failures (Chmielewski et al., 2023; Corrêa et al., 2019; Sahoo et al., 2021; Baseri et al., 2020; Aleksandrowicz et al., 2021; Ghassib et al., 2019).

In a study published in 2024, the evaluation of IL-1 polymorphisms was made under two groups and it was emphasized that there was a relationship between-IL-1 polymorphisms and PI only when-combined-with polymorphisms of other cytokines. It was stated that there may be a relationship-between-IL-1 polymorphisms and PI in the presence of heavy smoking, autoimmune diseases and chronic diseases (Santostasi et al., 2024). On the other hand, unlike IL-6, IL-1ß has been shown in different studies not to show similar levels in periodontal diseases. Furthermore, their levels are sometimes lower-than in mild-periodontitis (Aleksandrowicz et al., 2021). Additionally, IL-1ß levels, unlike other interleukins, are less in PI than-in periimplant-mucositis, suggesting possible-factors causing bone destruction (Corrêa et al., 2019).

IL-8 is-a-chemokine involved in the induction and development of acute and chronic inflammatory processes. Unlike many other cytokines, it has a distinct target specificity for the neutrophil, with only weak effects on other blood cells. IL-8 attracts and activates neutrophils in inflammatory regions (Bickel 1993). Neutrophils play a significant role in the pathogenesis of periodontal and peri-implant diseases. Their high concentrations can cause acute inflammation and infiltrate. This causes greater rates of bone loss, as seen in peri-implantitis. Studies have also reported that IL-8 SNPs are not individually associated-with-periodontitis. In this context, 8 polymorphisms of IL-8 were examined and it was revealed that there was no relationship between predisposition to periodontitis (Chmielewski et al., 2023). It was shown that there were differences in ethnic groups only in the *IL-8 rs4073* polymorphism, especially in Asian and mixed populations, and that there was no difference in the Caucasian population (Wang et al., 2016; Duarte et al., 2016; Faot et al., 2015). In addition, a study published in the Turkish population in 2022 reported that IL-8 coding polymorphisms did not create a significant change in IL-8 synthesis in periodontitis and PI patients (Turkmen et al., 2022).

IL-17 is a proinflammatory cytokine primarily for signaling-purposes and its production is stimulated by IL-23. It is produced by T lymphocytes (Chmielewski et al., 2023). The IL-23/IL-17 axis in immune system activity is known to be quite present in periodontal tissues. It is produced more especially in the presence of an extracellular pathogen. Th17 cells are the cornerstone of this axis and are a subset of CD4+ T cells. They are the cells responsible for coordinating the elimination of pathogens that damage periodontal tissues. This subset is distinguished primarily by the production of IL-17. IL-17 level is elevated in PI (Rodríguez-Montaño et al., 2025).

IL-17 stimulates fibroblasts mainly by binding to its receptor, which promotes the expression of further pro-inflammatory cytokines, one of which is RANKL, which activates osteoclasts and thus promotes bone erosion. Both periodontitis-and-PI are also common and widespread features (Kini et al., 2022). IL-23 stimulates IL-17 production by inducing the Th17 pathway in periodontal disease. There are six known IL-17 molecules, designated A to F. IL-17A is thought the main member-of-the IL-17 family and is therefore the-most-studied (Rosine et al., 2021).

When looking at studies examining PI, regarding *IL-17A rs10484879* polymorphism, a-study conducted in the Iranian population in 2013 reported a more frequent of the CC genotype than CA and AA in-patients-with periodontitis, PI and control groups. In addition, while the AA genotype was-not-detected in-the-chronic-periodontitis and periimplantitis groups, presence of the AA genotype was detected in the control group (Kadkhodazadeh et al., 2013a). Another case-control study published by the same group in 2013 primarily focused-on the genetic makeup of-IL-17. The-effect-of this polymorphism-on-chronic periodontal diseases was investigated. Two important differences were noted the two groups. CC-genotype was observed at a higher-frequency in the PI group. In terms of AA genotype, AA genotype was not observed in CP and PI patients (Kadkhodazadeh et al., 2013b).

The findings of the study published by Talib and Taha in 2024 contradict the studies conducted on the Iranian population. The-present-study observed a significantly-higher rate of periimplantitis in individuals with the AA or GA genotypes, i.e. genotypes containing the A allele, in *IL-17A rs2275913* gene polymorphism. It was stated that the-frequency-of the homozygous-genotype-AA in PI was much-higher than the frequency-of GG-genotype and G-allele. In addition, the effectiveness of the *IL-17A rs2275913* gene polymorphism in chronic periodontitis cases was taken into account, supporting the idea that it could be a beneficial determinations for-the pathogenesis-of-PI. It was also stated that *IL-17A rs2275913* gene polymorphism could serve as a prognostic biomarker for PI (Talib & Taha, 2024).

CONCLUSION

As a result of the studies obtained, although IL-6 is generally accepted as a proinflammatory cytokine and is known as an important mediator in acute and chronic inflammation processes in immune-related studies, we can state that more studies should be conducted in ethnic groups, especially on the *IL-6 rs1800795* polymorphism. In studies conducted on periodontitis, one of the periodontal diseases, the effectiveness of the *IL-6 rs1800795* polymorphism has-been demonstrated to a certain extent. However, there are few and limited studies on the effectiveness of approaches that include implant treatment, such as peri-implantitis. More studies with larger sample groups are needed on this subject.

On the other hand, in the studies conducted on other proinflammatory cytokines interleukins, the fact that IL-1 is pyrogen for other proinflammatory cytokines supports the idea that it is a significant proinflammatory cytokine for periodontal disease, and PI; while the variable results reported for IL-8 and IL-17 reveal the need for studies in different ethnic groups and larger samples.

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